DRUG RESEARCH AND DEVELOPMENT

– CASE SCENARIOS, DEVELOPMENT PROCESS, RISKS AND BENEFITS

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ABSTRACT

BACKGROUND AND AIMS. Drug development has been classically associated with large pharmaceutical companies developing 'blockbuster' drugs aimed at large patient populations through high market penetration and multiple indication life cycle management. Higher costs and lower output have rendered this model inefficient and unsustainable. The aims of this thesis were to assess: suitability of test procedures, benefit to risk profile during development, importance of stages of discovery and development for benefit/risk and entrepreneurship, expert judgement in making 'go/no-go' decisions, and implications for innovation.
METHODS. Literature review was used to identify why drugs fail and characterise drug regulation history. Examples of drugs in different development stages were critically reviewed for choice of test procedure and assessment of benefit/risk in context with knowledge and scientific expertise today. An 18-step model of drug discovery and development was defined. Using web-based questionnaires, health experts were asked the importance of each step for assessing benefit/risk, and entrepreneurial input. Individual judgement using real drug case scenarios was studied by scoring 'go/no-go' decisions on a Likert scale. Relative importance of assessment of risk versus entrepreneurial need was compared on the model. Influence of entrepreneurial characteristics on the expert assessments and on decision making was explored.
RESULTS. Drugs failed development for inefficacy and toxicity. Choice of test procedure confirmed anti-hypertensive and anti-asthmatic efficacy of K^+ channel openers in the laboratory, but these models were poor predictors of clinical potential. Alternative indications and potential routes of administration were left unexplored. Advances in molecular biology and screening have still failed to yield a product with full clinical potential. Retrospective case studies and prospective multicentre studies for an approved immunosuppressant proved valuable approaches for assessing risk of malignancy and risk during pregnancy. Identifying risk factors helps patients and carers in counselling to reach better outcomes. Health experts perceived toxicology, clinical trials, and pharmacovigilance most important for benefit/risk assessment. In contrast, drug discovery and later phases of development were of entrepreneurial importance. Results modelling revealed in-house entrepreneurial 'core' and external outsourcing opportunity. Experts showed marked variability in individual judgement for making 'go/no-go' decisions despite having the same information. Expert risk perception and decision making were not consistently influenced by entrepreneurial character. Optimised decision making was identified to be critical for effective drug development.
CONCLUSIONS. These findings reinforce the opinion that restructuring and opening up drug discovery and development to more external input is likely to increase the innovative capacity and efficiency of the whole drug discovery and development process.

KEY WORDS: drug discovery and development, benefit and risk, decision making, entrepreneurship, open innovation

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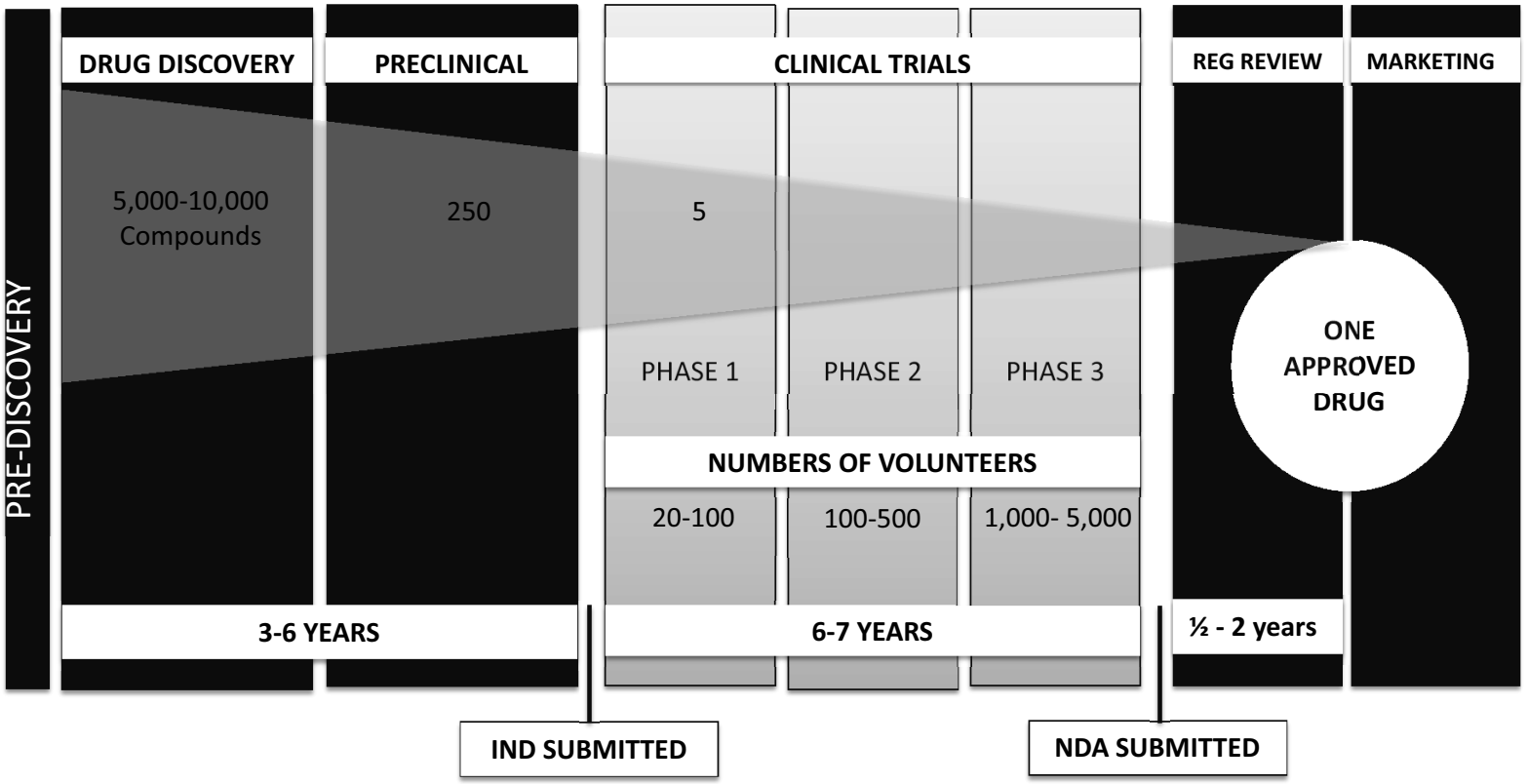

Figure 1

The drug discovery and development process (adapted from Pharmaceutical Industry Profile, 2009)

Drug discovery
1) Selection and validation of target areas for drug research - how and why a certain drug mechanism or target is chosen and validated?
2) Drug synthesis and drug characterisation
3) Pharmacology: drug screening of potential development candidates, efficacy evaluation and preclinical safety
4) Drug formulation, analysis and stability for entry into man
5) Costs assessment - is there sufficient market potential and profit to justify drug development?
6) Toxicology of a drug including acute/subacute/chronic toxicology, teratology, mutagenicity, carcinogenicity
Drug development
7) Pharmacokinetics: preclinical (and later clinical drug absorption, distribution, metabolism and excretion)
8) Regulatory processes: conducting clinical trials, compiling drug dossier, submission, regulatory assessment
9) Phase 1 / First Time in Humans: pharmacokinetics, early pharmacodynamics
10) Phase II early: proof of concept and efficacy
11) Phase II late and Phase III: establishing dose relationship of effect and against comparator
12) Pharmaceutical processes: scale up, packaging and distribution
13) Sales and marketing of approved drug in the market place
14) Safety and pharmacovigilance of marketed drug
15) Post-marketing support of marketed drug with scientific and medical information
16) Publication of clinical experience with newly approved drug
17) Pharmacoeconomics of new drug, price reimbursement etc
18) Public's and patient's perception of new drug

Figure 2
Drug discovery and development – 18-step model for analysis (Cowlrick et al, 2009)

drug scenarios based on Papers I to IV were placed before each employee and the variability in judgement for each go/no-go decision was assessed to see if it was influenced by any demographic factors or entrepreneurial characters. The findings were then reviewed in the light of how decisions are taken in industry and some of the options which are available to industry to optimise the decision making process to create more value.

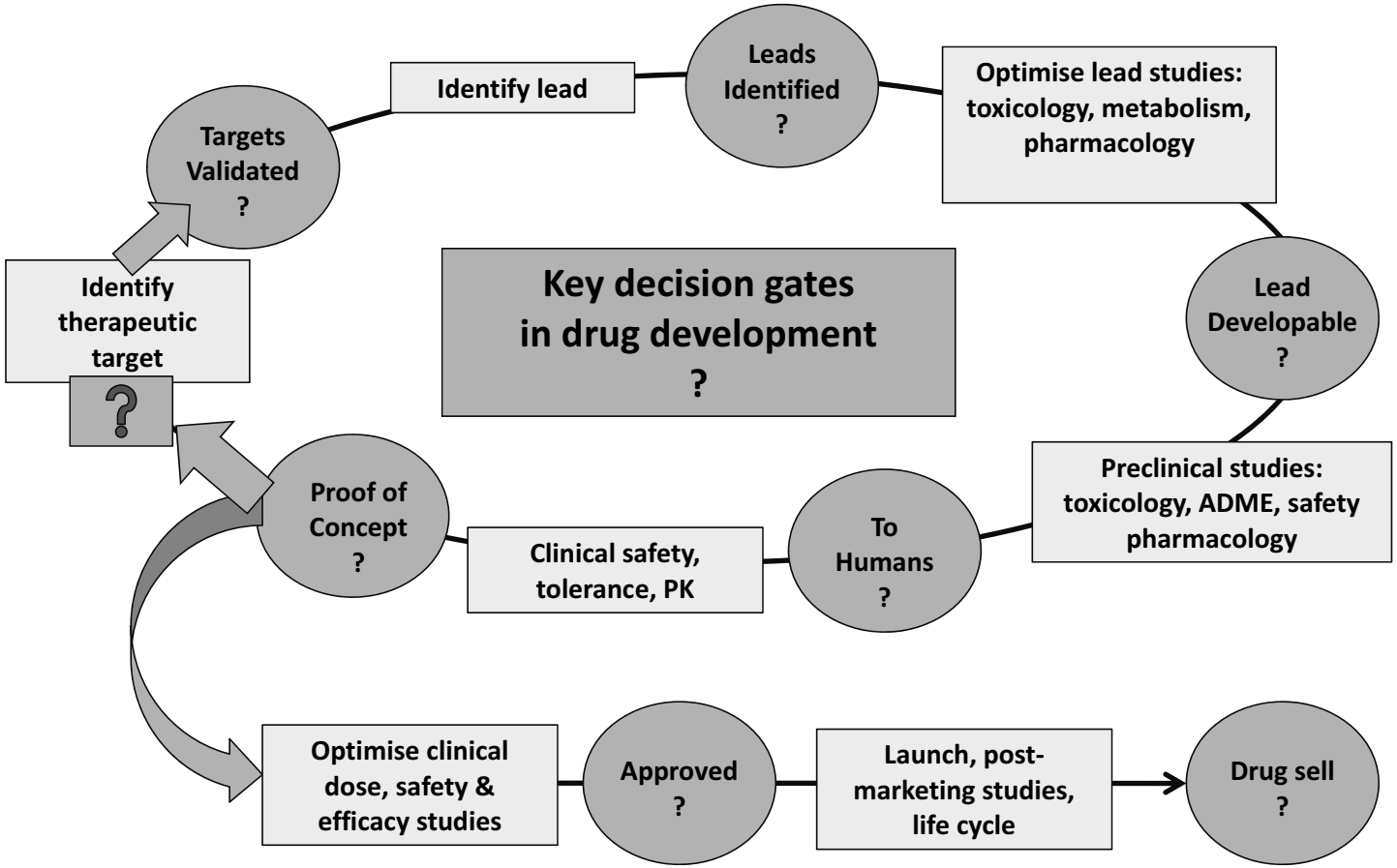

Figure 3

Key decision gates in drug development (adapted from Pritchard, 2003)

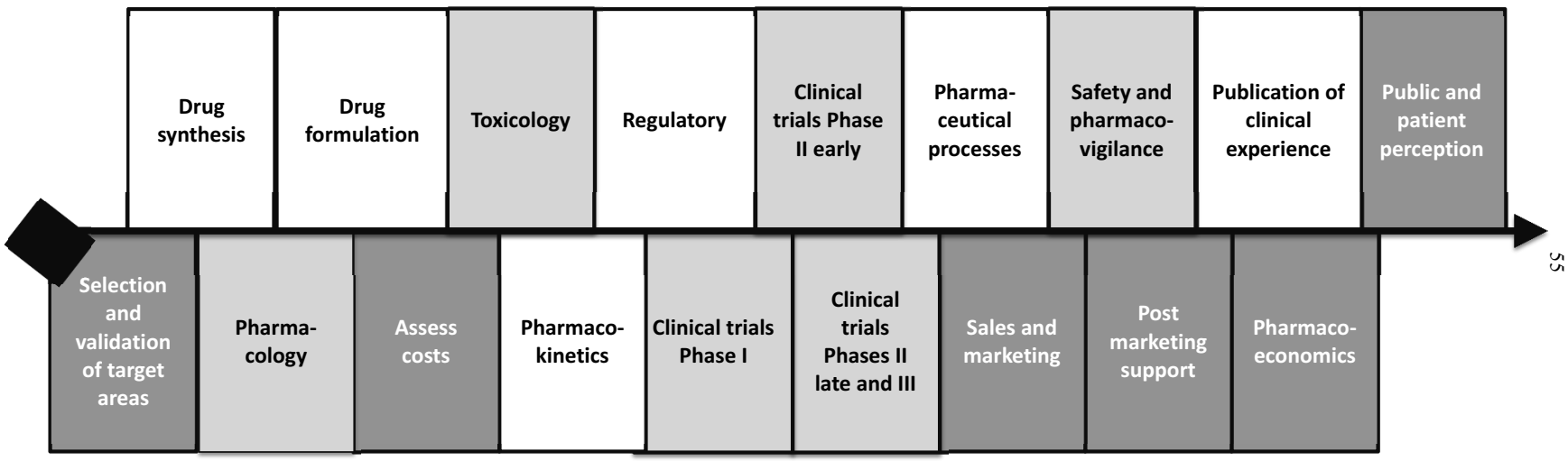

Figure 4

A model of drug discovery and development showing outsource potential and core processes

(Overlapping boxes represent drug discovery, development and marketing processes indicating these processes are non-discrete often running in parallel. Dark grey boxes with white text are those processes perceived to be highly important for entrepreneurial attitude and light grey boxes with black text are those processes perceived to be highly important for assessment of benefit and risk. Dark grey boxes/processes might be considered core/in-house skills while light grey boxes/processes are well regulated, are often the reasons why drugs fail, and some can be outsourced.)

CONCLUDING REMARKS

The thesis began with the general hypothesis:

'Over the last few decades there has been increased emphasis placed on drug safety (and efficacy) resulting in increased drug development costs which have forced the pharmaceutical industry to reconsider their role and approach in developing new chemical entities'.

The information gathered from literature review, summarised in the Introduction of this thesis and later discussed, strongly supports this hypothesis. Worse still, drug development appears critically ill and inefficient. The present model of drug development no longer delivers new medicines capable of providing return on investment to fund future research. In an effort to restructure, industry has preoccupied itself with mergers and acquisitions which provide stakeholders with short-term benefit. Longer-term, at best, innovation remains flat. Industry has also begun to open up with increased outsourcing and partnerships. However, the model proposed for drug development in the present work suggests industry can go much further. As part of this change, the entrepreneurship potential of researchers and other professionals could be nurtured and strengthened, not least in drug discovery and during the latter stages of sales, marketing and pharmacoeconomics. Opening the whole process to increased external expert input also arms decision makers with the knowledge and wisdom to adopt more objective strategies to address drug target and business profiles. This thesis shows that drug regulations have developed largely in response to drug disasters. Despite the complex nature of these regulations, drugs still frequently fail for reasons of inefficacy and toxicity prior to approval, and for toxicity during marketing. Regulatory agencies have also acknowledged 'delivery failure' by taking initiatives to address this situation. They stand as a key stakeholder and agent of change if patients are to be provided with novel and effective medicines.

The following questions were set under this general hypothesis:

- Were the choices of test procedures (preclinical test system and clinical trials) years ago appropriate for identifying/evaluating novel drugs and how do those processes compare with today?

Critique of the methodology adopted to evaluate drug candidates (K+ channel openers as anti-hypertensives and anti-asthmatics) over the last 20 years using real examples shows that the models were appropriate to demonstrate efficacy in the laboratory. However, the predictive clinical value of these procedures is far from ideal. R&D units are under pressure to produce a lead candidate quickly so that appropriate disease models may not be optimally developed, and potential indications and routes of administration left unexplored. Technology has advanced and with it a better understanding of molecular targets and drug discovery. However, this improving scenario has still failed to yield an increase in clinically valuable products today although some candidates look promising. Review of the methodology adopted to assess safety of immunosuppressants during pregnancy and for malignancy risk after drug approval showed the approaches to be simple, effective and to enhance the balance of benefit to risk assessment favouring benefit for patients. This underlines the role and value of continued surveillance, retrospective case studies and prospective clinical trials.

- Which factors within drug R&D past and present confer increased knowledge and awareness for future drug research?

Drug development has successfully been built upon a 'blockbuster model' for many years whereby a 'me-too drug' or a drug with a new indication was aggressively marketed to large patient populations and rewarded by handsome returns on investment. Despite advancements in molecular biology and characterisation of target receptors, new drug indications have become difficult to exploit. This could be because new indications are more difficult to develop than before and/or perhaps the innovative potential has largely disappeared. This work suggests some of the latter and that stakeholders need to address this deficit. The present findings also argue that opening the whole drug development process up to more external influence will result in better decision making for future research.

- What is the nature of risk for potential candidates in drug R&D based on real case scenarios?

The nature of risk should always be balanced against benefit in context with the target disease. In particular, the risk of cardiovascular events was considered too great for drug candidates studied in this thesis. Conversely, transplant offers much benefit and a medical solution for end-stage organ failure despite a greatly increased risk for malignancy with life-long immunosuppression. The challenge to decision makers is to assess the net benefit

(against the risk) as early as possible in drug development and develop the best drugs further. The resultant should be a more efficient drug process which society can afford.

- How important is innovation and entrepreneurship in drug discovery and R&D and which factors influence this perception?

Without innovation and entrepreneurship industry would die. This thesis suggests that this is indeed the case. Invited experts, as decision makers for several drug case scenarios, also indicated that drug discovery and the latter stages of development especially require entrepreneurial input. Many small R&D units appear more efficient than fewer larger 'Big Pharma' players. Proposals to correct this inefficiency are restructuring of Big Pharma R&D, exploitation of open innovation, returning power to entrepreneurs, and enabling more objective decision making. There is already considerable evidence that these changes are taking place and do improve efficiency.

- How is a go or no-go decision made during drug R&D?

Effective go/no-go decisions are the pillar of efficient drug development. Despite identification of a drug target profile and business profile, decisions must be made with incomplete information and with many unknowns. The present drug case scenarios show that this process involves marked individual variability in judgement. Techniques are available to facilitate group decision making but human judgement is the dominant technique exercised by most companies. Companies, regulatory bodies, and other stakeholders might prosper by opening their doors to others gifted with more magical insight.

- How can one consider value and benefit versus risk for new drugs against costs of development and other limiting factors?

One can argue that faced with life-threatening disease, for drugs which are highly efficacious, costs become increasingly less relevant. One should also never forget that no drug comes without the risk of side effects. There are a number of methods used to assess or even justify cost of therapy which were not considered in this work. Evidence in this thesis does support that clinical efficacy, therapeutic index, and tolerability are important drug profile properties to consider for candidate development. The medical need and the potential market should also be evaluated. Drug development is so costly that the candidate profile should

continuously be addressed against the target criteria throughout the development process. Stakeholders and society at large are under enormous pressure to review how drugs are developed to restore innovation and efficiency. Changes in legislation and changes in patent regulation are two of the many areas open to debate if patients are to continue to receive novel therapies for acute and chronic diseases.